Exhibit 1

[redacted]

THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD.,)

Plaintiff,) C.A. No. 21-1015 (JLH)

vs.) [redacted]

SAREPTA THERAPEUTICS, INC.,) [redacted]

Defendant.)

_____)

AND RELATED CROSS-CLAIM.)

_____)

VIDEO DEPOSITION OF STEVEN F. DOWDY, PH.D.

VOLUME II

SEPTEMBER 12, 2024

Reported by: Rosalie A. Kramm, CSR No. 5469, RPR, CRR

with the noticing attorney.

MS. WILLIAMSON: Good morning. Amanda Williamson and Mike Sikora on behalf of Nippon Shinyaku and NS Pharma.

MR. RAICH: Bill Raich of Finnegan for Sarepta and UWA. With me today is my colleague, Yoonjin Lee, also with Finnegan.

THE VIDEOTAPE OPERATOR: Thank you.

* * *

STEVEN F. DOWDY, PH.D.,

having been first duly sworn, testified as follows:

EXAMINATION (continued)

BY MS. WILLIAMSON:

Q. Good morning, Dr. Dowdy.

A. Good morning.

Q. As you know, this is your second deposition in this matter.

A. Yes.

(Exhibit 14 was marked for identification.)

BY MS. WILLIAMSON:

Q. And you have in front of you an exhibit marked No. 14. Is this the rebuttal report that you submitted in this matter on August 14th, 2024?

A. Yes, it's the supplemental rebuttal expert

report.

Q. So if I refer to it as the supplemental report, you'll understand what I'm --

A. Yes.

Q. -- speaking about? Because there are multiple reports in this matter.

And you would agree with me that the -- that your supplemental report was submitted in rebuttal to supplemental reports submitted by Dr. Hastings and Dr. Wood.

A. Yes.

Q. As an initial matter, you would agree that a POSA would not have been certain that ASOs potentially within the UWA patent genus would, in fact, induce exon 53 skipping.

A. No, I disagree.

Q. So you could say with certainty that every candidate potentially within the genus would induce exon 53 skipping?

A. No. I would say -- I have said that -- that there is a high probability that if you're within the genus, that you will, in fact, induce exon 53 skipping.

Q. But you would agree that there is not a certainty that a potential ASO within the genus will induce skipping without actual testing?

A. As I said, there is a high probability that any oligo -- sorry. Any oligo that fulfills the criterion in claim 1 that the POSA would see, would induce exon 53 skipping.

Q. And a high probability is not a certainty; isn't that true?

A. A high probability is close to certainty, but no, it is not certainty.

Q. If you could turn to paragraph 13 of your expert report, your supplemental report. Excuse me.

A. I have it in front of me.

Q. You state that, in the last paragraph -- the last sentence of that paragraph on page 7, "A POSA would have been able to visualize each claim to PMO based on this structure-function relationship."

Do you see that?

A. Yes, I do.

Q. Are you referring to the structure-function relationship derived from the purported hotspot, or substantial overlap with purported hotspot that you've identified?

A. As I've written in front of that, I'm -- that sentence is related to the claims of the '851 patent that a POSA would see 168 well-defined oligonucleotides.

Q. Yes. And then you say, "A POSA would have been

able to visualize each claimed PMO based on this structure-function relationship."

What is that structure-function relationship?

A. The criterion laid out in Claim 1.

Q. And so if we then turn to paragraph 15, are those criteria laid out here as: antisense oligonucleotides, 20 to 31 bases, comprising a base sequence that is 100 percent complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, and the 12 consecutive bases of SEQ. ID 195, in connection with the uracil bases are thymine bases, and where the antisense oligonucleotide is a morpholino antisense oligonucleotide?

A. It induces exon 53 skipping, yes. That's what I'm referring to.

Q. But induces -- induces skipping is not part of the -- or that's not part of the structure. That's the function, right?

A. Yes.

Q. The claim does not reference a hotspot; is that correct?

A. Hot -- I'm sorry. I woke up this morning, and I had a little bit of a frog in my throat, so it might be a little -- until my voice gets going.

A hotspot is a molecular biology slang for an

antisense oligonucleotide with 12 bases within SEQ. ID 195 -- strike that.

To determine whether there is a 12-base sequence within SEQ. ID 195 that induces skipping on its own, you would have to test oligonucleotides to find that one, right?

A. Claim 1 does not direct you to look at 12 mers antisense oligonucleotides. It directs you to look at 20 to 31. It is -- the structural elements of Claim 1 really define and hone down to 168 species.

So whether 12 did or did not, or 19 did or did not, is outside the structural requirements for Claim 1.

So I'm not saying that there is not an oligo within the hotspot that could or could not induce skipping that doesn't fulfill all of the criterion. It doesn't matter, because the claim says if you follow these rules, you have a very high probability of inducing skipping. It doesn't mean there's others that will induce skipping that don't follow the rules that are inside or outside the hotspot. It just says you have a high probability of finding a splicer within the confines of Claim 1.

MS. WILLIAMSON: Is now a good time for a break?

MR. RAICH: Sure.

THE VIDEOTAPE OPERATOR: Going off the record at 12:56 p.m.

(Recess was taken.)

THE VIDEOTAPE OPERATOR: We are back on the record at 1:13 p.m.

BY MS. WILLIAMSON:

Q. Dr. Dowdy, could you please turn to paragraph 119 of your supplemental report.

A. Paragraph 119?

Q. Yes, please.

A. I have it in front of me.

Q. In this paragraph you're responding to Dr. Hastings' opinions; is that correct?

A. I'd have to refresh myself here. Just a minute.

Okay. Sorry. I read through that paragraph. I'm familiar now.

Q. Is that characterization correct, are you responding to Dr. Hastings' arguments in this paragraph?

A. Yes, I am.

Q. And in particular, you're opining on her reliance on certain data, certain exon 3 and 43 data cited in her report.

A. Correct, as written here.

Q. And you state that, "The data relating to exon

43 was not available in June 2005, and thus could not reflect the understanding of a POSA as of that time."

Is that correct?

A. Yes, I wrote that.

Q. So you would agree in your view, data that was not available in June 2005 would not reflect the understanding of a POSA at that time.

A. Correct. All of that is after the fact in terms of ascertaining the value of that.

Q. Let's turn back to paragraph 25 and 26 --

A. Of my --

Q. -- of your supplemental report.

A. Thank you. 25, 26?

Q. Uh-huh.

A. I have it in front of me. Just give me a second to refresh. Yes.

Q. And in this paragraph you're discussing the prosecution history of U.S. Patent No. 9,024,007.

A. Yes.

Q. All right. If I refer to that as the "'007 patent," you'll understand what I'm talking about?

A. Yes.

Q. And according to your report, the '007 patent claims priority to the same patent application as the '851 patent and the other asserted Wilton patents.

A. Correct.
Q. And you agree with that statement?
A. Yes, I do.
Q. And here in this paragraph you rely on portions of the prosecution history for the '007 patent in support of your opinions in your supplemental rebuttal report; is that correct?
A. Yes.
Q. And, in particular, you rely on the '007 patent's prosecution history to support your argument that the term "morpholino antisense oligonucleotide" refers to the chemical structure of the oligonucleotide backbone in which six-membered morpholine rings replace ribose, and nucleotides are joined by phosphorodiamidate linkages.
A. Correct, in paragraph 26.
Q. Why do you believe it's appropriate to rely on the UWA and Sarepta's statements to the patent office in the '007 patent's prosecution history?
A. Why do I believe that it's okay?
Q. Yes. Or not -- yes. Why do you believe it's appropriate? Why do you believe it is reliable evidence in support of your opinion?
A. I think it's another example of using -- of the word "morpholino" specifically meaning a

Exhibit 2

THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (JLH) [redacted]
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC. Plaintiff/Counter-Defendants.	

SUPPLEMENTAL REBUTTAL EXPERT REPORT OF STEVEN F. DOWDY, Ph.D.

[redacted]

14. Dr. Hastings' supplemental arguments do not change my opinion. As discussed below, Dr. Hastings' contention that the claim scope of the Wilton Patents remains "tremendous" even under the Court's clarified and/or amended construction (which indisputably narrowed the scope of the claims) is unsupported by the intrinsic evidence and the state of the art. As in her Opening Report, Dr. Hastings artificially inflates the scope of the Wilton Patent claims by disregarding the experience and common sense of the POSA, as well as the disclosure of the Wilton Patents. Similarly, her supplemental written description analysis disregards structural features recited in the claims of the Wilton Patents that confer the claimed function of inducing exon 53 skipping. Additionally, while Dr. Hastings continues to allege "unpredictability" in the art, she ignores key evidence, and much of the evidence she cites actually weighs in favor of predictability within the exon 53 hot spot. Thus, I maintain my opinion that the Wilton Patents satisfy the written description requirement.

1. The Claims of the Wilton Patents Are Narrow in Scope

a. The Claims of the Wilton Patents Are Directed to a Limited Group of Structurally Defined PMOs

15. Each of the claimed oligonucleotides of the Wilton Patents shares the following common structural features: (1) "antisense oligonucleotide"; (2) "20 to 31 bases"; (3) "comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA" (meaning that the base sequence of the entire oligonucleotide is 100% complementary to its target region; *see supra* § III.B); (4) "the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195)"; (5) "in which uracil bases are thymine bases"; and (6) "wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide." *See* Dowdy Reb. Rep. ¶56. In the case

[redacted]

of the '851 Patent, the claimed target region is confined to nucleotides +23 to +69 of exon 53 of the human dystrophin pre-mRNA, as construed by the Court. *Id.*

16. These structural requirements collectively identify a discrete group of target regions and a limited number of corresponding PMOs. Indeed, as Dr. Hastings acknowledges (Hastings Supp. Rep. ¶¶48-50), the claims of the Wilton Patents encompass only "dozens" of target regions—***168*** target regions for the '851 Patent and ***330*** target regions for the'590 and '827 Patents. Tables 1 and 2 below summarize the target regions encompassed by each of the Wilton Patents.

ASO Length	Target Region Coordinates in Exon 53 of the Human Dystrophin Pre-mRNA	Number of Unique Target Regions
20	(+23+42), (+24+43), (+25+44), (+26+45), (+27+46), (+28+47), (+29+48), (+30+49), (+31+50), (+32+51), (+33+52), (+34+53), (+35+54), (+36+55)	14
21	(+23+43), (+24+44), (+25+45), (+26+46), (+27+47), (+28+48), (+29+49), (+30+50), (+31+51), (+32+52), (+33+53), (+34+54), (+35+55), **(+36+56)**[2]	14
22	(+23+44), (+24+45), (+25+46), (+26+47), (+27+48), (+28+49), (+29+50), (+30+51), (+31+52), (+32+53), (+33+54), (+34+55), (+35+56), (+36+57)	14
23	(+23+45), (+24+46), (+25+47), (+26+48), (+27+49), (+28+50), (+29+51), (+30+52), (+31+53), (+32+54), (+33+55), (+34+56), (+35+57), (+36+58)	14
24	(+23+46), (+24+47), (+25+48), (+26+49), (+27+50), (+28+51), (+29+52), (+30+53), (+31+54), (+32+55), (+33+56), (+34+57), (+35+58), (+36+59)	14
25	(+23+47), (+24+48), (+25+49), (+26+50), (+27+51), (+28+52), (+29+53), (+30+54), (+31+55), (+32+56), (+33+57), (+34+58), (+35+59), **(+36+60)**[3]	14
26	(+23+48), (+24+49), (+25+50), (+26+51), (+27+52), (+28+53), (+29+54), (+30+55), (+31+56), (+32+57), (+33+58), (+34+59), (+35+60), (+36+61)	14
27	(+23+49), (+24+50), (+25+51), (+26+52), (+27+53), (+28+54), (+29+55), (+30+56), (+31+57), (+32+58), (+33+59), (+34+60), (+35+61), (+36+62)	14

[2] NS's Viltepso® (viltolarsen) targets nucleotides +36 to +56 of exon 53 of the human dystrophin pre-mRNA. *See* Dowdy Op. Rep. ¶139.

[3] Sarepta's Vyondys 53® (golodirsen) targets nucleotides +36 to +60 of exon 53 of the human dystrophin pre-mRNA. *See* Dowdy Op. Rep. ¶133.

[redacted]

ASO Length	Target Region Coordinates in Exon 53 of the Human Dystrophin Pre-mRNA	Number of Unique Target Regions
28	(+23+50), (+24+51), (+25+52), (+26+53), (+27+54), (+28+55), (+29+56), (+30+57), (+31+58), (+32+59), (+33+60), (+34+61), (+35+62), (+36+63)	14
29	(+23+51), (+24+52), (+25+53), (+26+54), (+27+55), (+28+56), (+29+57), (+30+58), (+31+59), (+32+60), (+33+61), (+34+62), (+35+63), (+36+64)	14
30	(+23+52), (+24+53), (+25+54), (+26+55), (+27+56), (+28+57), (+29+58), (+30+59), (+31+60), (+32+61), (+33+62), (+34+63), (+35+64), (+36+65)	14
31	(+23+53), (+24+54), (+25+55), (+26+56), (+27+57), (+28+58), (+29+59), (+30+60), (+31+61), (+32+62), (+33+63), (+34+64), (+35+65), (+36+66)	14
Total		**168**

Table 1. Target Regions Encompassed by the Claims of the '851 Patent

ASO Length	Target Region Coordinates in Exon 53 of the Human Dystrophin Pre-mRNA	Number of Unique Target Regions
20	(+15+34), (+16+35), (+17+36), (+18+37), (+19+38), (+20+39), (+21+40), (+22+41), (+23+42), (+24+43), (+25+44), (+26+45), (+27+46), (+28+47), (+29+48), (+30+49), (+31+50), (+32+51), (+33+52), (+34+53), (+35+54), (+36+55)	22
21	(+14+34), (+15+35), (+16+36), (+17+37), (+18+38), (+19+39), (+20+40), (+21+41), (+22+42), (+23+43), (+24+44), (+25+45), (+26+46), (+27+47), (+28+48), (+29+49), (+30+50), (+31+51), (+32+52), (+33+53), (+34+54), (+35+55), **(+36+56)**	23
22	(+13+34), (+14+35), (+15+36), (+16+37), (+17+38), (+18+39), (+19+40), (+20+41), (+21+42), (+22+43), (+23+44), (+24+45), (+25+46), (+26+47), (+27+48), (+28+49), (+29+50), (+30+51), (+31+52), (+32+53), (+33+54), (+34+55), (+35+56), (+36+57)	24
23	(+12+34), (+13+35), (+14+36), (+15+37), (+16+38), (+17+39), (+18+40), (+19+41), (+20+42), (+21+43), (+22+44), (+23+45), (+24+46), (+25+47), (+26+48), (+27+49), (+28+50), (+29+51), (+30+52), (+31+53), (+32+54), (+33+55), (+34+56), (+35+57), (+36+58)	25
24	(+11+34), (+12+35), (+13+36), (+14+37), (+15+38), (+16+39), (+17+40), (+18+41), (+19+42), (+20+43), (+21+44), (+22+45), (+23+46), (+24+47), (+25+48), (+26+49), (+27+50), (+28+51), (+29+52), (+30+53),	26

[redacted]

ASO Length	Target Region Coordinates in Exon 53 of the Human Dystrophin Pre-mRNA	Number of Unique Target Regions
	(+31+54), (+32+55), (+33+56), (+34+57), (+35+58), (+36+59)	
25	(+10+34), (+11+35), (+12+36), (+13+37), (+14+38), (+15+39), (+16+40), (+17+41), (+18+42), (+19+43), (+20+44), (+21+45), (+22+46), (+23+47), (+24+48), (+25+49), (+26+50), (+27+51), (+28+52), (+29+53), (+30+54), (+31+55), (+32+56), (+33+57), (+34+58), (+35+59), **(+36+60)**	27
26	(+9+34), (+10+35), (+11+36), (+12+37), (+13+38), (+14+39), (+15+40), (+16+41), (+17+42), (+18+43), (+19+44), (+20+45), (+21+46), (+22+47), (+23+48), (+24+49), (+25+50), (+26+51), (+27+52), (+28+53), (+29+54), (+30+55), (+31+56), (+32+57), (+33+58), (+34+59), (+35+60), (+36+61)	28
27	(+8+34), (+9+35), (+10+36), (+11+37), (+12+38), (+13+39), (+14+40), (+15+41), (+16+42), (+17+43), (+18+44), (+19+45), (+20+46), (+21+47), (+22+48), (+23+49), (+24+50), (+25+51), (+26+52), (+27+53), (+28+54), (+29+55), (+30+56), (+31+57), (+32+58), (+33+59), (+34+60), (+35+61), (+36+62)	29
28	(+7+34), (+8+35), (+9+36), (+10+37), (+11+38), (+12+39), (+13+40), (+14+41), (+15+42), (+16+43), (+17+44), (+18+45), (+19+46), (+20+47), (+21+48), (+22+49), (+23+50), (+24+51), (+25+52), (+26+53), (+27+54), (+28+55), (+29+56), (+30+57), (+31+58), (+32+59), (+33+60), (+34+61), (+35+62), (+36+63)	30
29	(+6+34), (+7+35), (+8+36), (+9+37), (+10+38), (+11+39), (+12+40), (+13+41), (+14+42), (+15+43), (+16+44), (+17+45), (+18+46), (+19+47), (+20+48), (+21+49), (+22+50), (+23+51), (+24+52), (+25+53), (+26+54), (+27+55), (+28+56), (+29+57), (+30+58), (+31+59), (+32+60), (+33+61), (+34+62), (+35+63), (+36+64)	31
30	(+5+34), (+6+35), (+7+36), (+8+37), (+9+38), (+10+39), (+11+40), (+12+41), (+13+42), (+14+43), (+15+44), (+16+45), (+17+46), (+18+47), (+19+48), (+20+49), (+21+50), (+22+51), (+23+52), (+24+53), (+25+54), (+26+55), (+27+56), (+28+57), (+29+58), (+30+59), (+31+60), (+32+61), (+33+62), (+34+63), (+35+64), (+36+65)	32
31	(+4+34), (+5+35), (+6+36), (+7+37), (+8+38), (+9+39), (+10+40), (+11+41), (+12+42), (+13+43), (+14+44), (+15+45), (+16+46), (+17+47), (+18+48), (+19+49), (+20+50), (+21+51), (+22+52), (+23+53),	33

[redacted]

ASO Length	Target Region Coordinates in Exon 53 of the Human Dystrophin Pre-mRNA	Number of Unique Target Regions
	(+24+54), (+25+55), (+26+56), (+27+57), (+28+58), (+29+59), (+30+60), (+31+61), (+32+62), (+33+63), (+34+64), (+35+65), (+36+66)	
Total		**330**

Table 2. Target Regions Encompassed by the Claims of the '590 and '827 Patents

17. The limited number of discrete target regions encompassed by the claims of the Wilton Patents limits the number of candidate PMOs covered by the claims, particularly as the claims recite a series of additional structural features for these PMOs. Specifically, the claims require a specific length ("20 to 31 bases"), require 100% complementarity to consecutive bases of the target region over their complete length; require a particular backbone chemistry ("morpholino"); and require a particular type of base ("thymine" in place of "uracil"). These structural features would have allowed a POSA to visualize a limited group of ASOs corresponding to each target region. For example, when considering the naturally occurring bases, there are only ***168*** candidate nucleobase sequences that fall within the claim scope of the '851 Patent, and only ***330*** candidate nucleobase sequences that fall within the claim scope of the '590 and '827 Patents.

18. As in my Rebuttal Report, I refer to these as "candidate" ASOs that potentially fall within the claim scope of the Wilton Patents. *See* Dowdy Reb. Rep. ¶59. And the number of ASOs that meet all of the claimed structural limitations and therefore *potentially* fall within the scope of the claims of the Wilton Patents would have been understood to be largely coextensive with the number of ASOs that induce exon 53 skipping and *actually* fall within the claim scope of the Wilton Patents, as these ASOs target the exon 53 hot spot with 100% complementarity. *See infra* § IV.A.2.a; '851 Patent, Table 39; Dowdy Op. Rep. § V.C.4.b. Further, a POSA would have

[redacted]

been able to use routine techniques, including those disclosed in the Wilton Patents, to confirm that exon 53 skipping was actually induced. *See* Dowdy Reb. Rep. §§ V.A.2.d, V.B.2.b-c; '851 Patent, cols. 32-33; Dowdy Op. Rep. § V.C.5. Notably, every ASO having the claimed structural requirements made and tested to date induces exon 53 skipping, and Dr. Hastings and Dr. Wood identify no contrary evidence. *See* Dowdy Reb. Rep. § V.A.2.c. In sum, a POSA would have understood that only a limited number of candidate PMOs meet the structural limitations of the claims, and moreover that the actual number of PMOs covered by the claims is likewise small.

b. Dr. Hastings' Contrary Claim Scope Analysis Is Incorrect

19. Dr. Hastings contends that "[e]ven after the Court's revised construction, it remains my opinion that the [Wilton] Patent claims are drawn to a broad genus that encompasses a tremendous number of antisense oligonucleotide species." Hastings Supp. Rep., ¶44. According to Dr. Hastings, the claims of the Wilton Patents may encompass "billions" of ASOs because the claims are not limited to "one exact length" with "one exact sequence of bases" and instead allow for "possible chemical variations." *Id.* ¶¶45-81.

20. As an initial matter, I understand that the written description requirement does not demand a nucleotide-by-nucleotide recitation of the entire genus of claimed genetic materials. *See* Dowdy Reb. Rep. ¶12. Instead, the written description requirement can be satisfied by the disclosure of structural features common to the members of the genus. *Id.*, ¶11. That the claims of the Wilton Patents are not limited to "one exact length" with "one exact sequence of bases" is therefore irrelevant to assessing the written description of the Wilton Patents. As discussed in my Rebuttal Report and further herein, the proper inquiry, which focuses on the disclosure of structural features common to the members of the genus, confirms that the Wilton Patents satisfy the written description requirement. *See* Dowdy Reb. Rep. § V.A; *see infra* § IV.A.2.a.

[redacted]

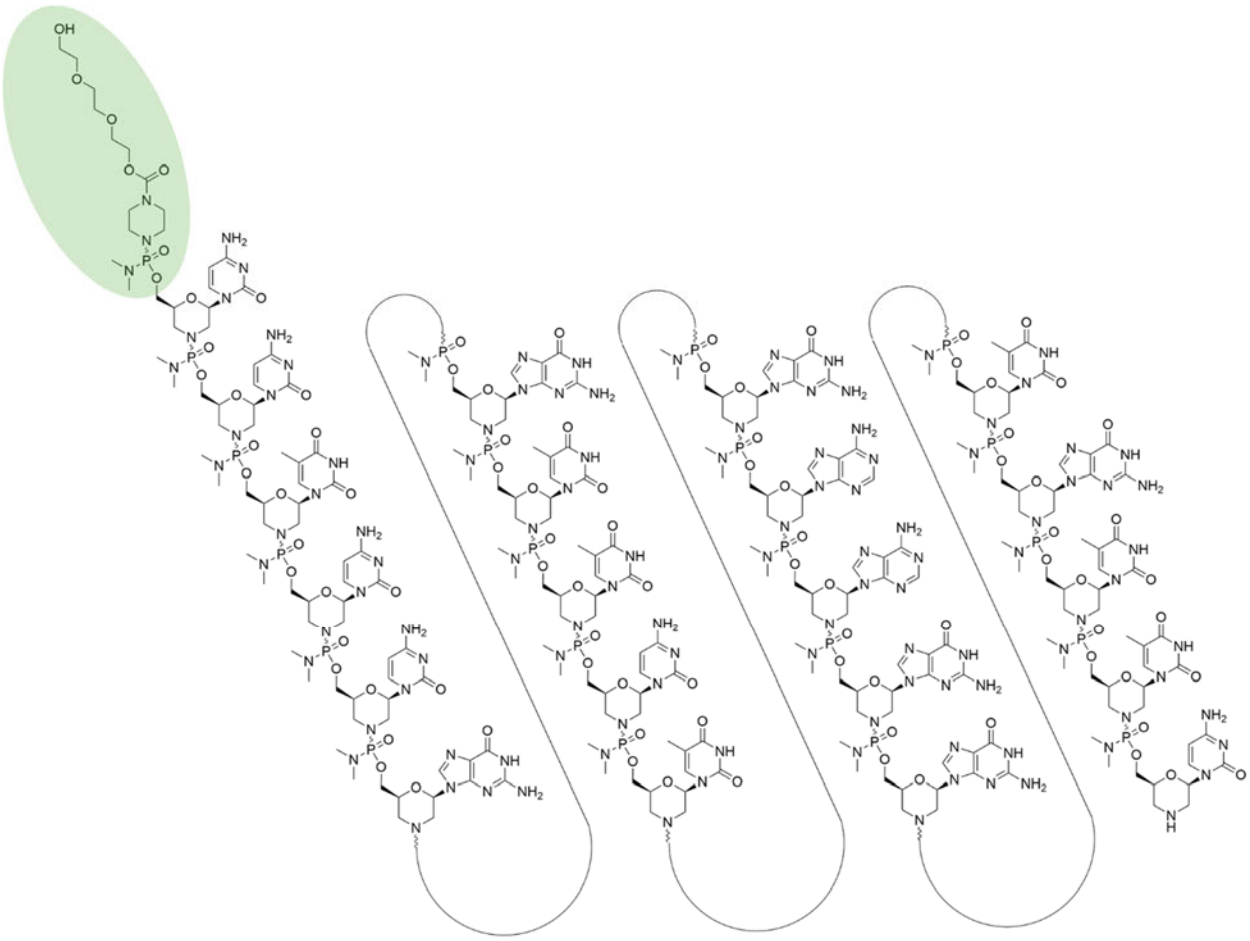

Figure 5. Exemplary Candidate PMO with a 5'-End Modification (**TEG**)

61. A POSA would have expected that most candidate PMOs, if not all, would induce exon 53 skipping because they target the exon 53 hot spot identified by Dr. Wilton and his co-inventors, regardless of whether they contain modified bases and/or an end modification. Dowdy Reb. Rep. ¶¶67-68; *see also id.*, ¶¶69-74. For example, the structural features recited in claim 1 of the '851 Patent identify candidate PMOs directed to nucleotides +23 to +66 of exon 53 of the human dystrophin pre-mRNA, meaning that the target region for each candidate PMO falls within the exon 53 hot spot. *See supra* § IV.A.1.a.

62. The specification of the Wilton Patents provides empirical evidence supporting the correlation between the structures recited in the claims and the function of inducing exon 53

skipping. *See* Dowdy Reb. Rep. ¶¶69-72. As I explained previously, the specification evaluated four overlapping ASOs, H53A(+23+47), H53A(+39+62), H53A(+45+69), and H53A(+39+69), that target a discrete region within exon 53 of the human dystrophin pre-mRNA. *See* '851 Patent, Table 39. All of these ASOs are reported to induce exon 53 skipping, and collectively they establish a hot spot for exon skipping from positions 23 to 69. *Id.* A POSA would have expected that the claimed PMOs, which target this hot spot, would similarly induce exon 53 skipping.

63. This correlation is strengthened by the Court's amended claim construction, which clarifies that the base sequence of each claimed ASO must be 100% complementary to consecutive bases of its exon 53 target region throughout the entire length of the ASO. *See supra* § III.B. As of June 2005, a POSA would have known that exon skipping is mediated by "a true antisense mechanism." Dowdy Reb. Rep. ¶47; Errington 2003, 525. By that time, studies had shown that an ASO with 100% complementarity generally induces more robust exon skipping than a corresponding ASO lacking 100% complementarity. *E.g.*, Errington 2003, 525 ("20- to 100- fold higher concentrations of mismatched 2'OMeAOs were required to induce exon 19 skipping compared with the analogous perfectly matched 2'OMeAOs."). The structural requirement of 100% complementarity would have reinforced the POSA's understanding that most, if not all, candidate PMOs would induce exon 53 skipping.

b. Dr. Hastings' Structure-Function Analysis Is Misguided

64. In her Supplemental Report, Dr. Hastings repeats many of the arguments that she previously raised in her Opening Report. *See* Hastings Supp. Rep. ¶¶114-126. Although I have addressed substantively the same arguments in my Rebuttal Report (*see* Dowdy Reb. Rep. § V.A.2.d), I provide my supplemental opinions on three of Dr. Hastings' specific arguments: (1) the alleged lack of common structural features based on base sequences; (2) alleged unpredictability; and (3) alleged lack of data obtained from claimed PMOs.

[redacted]

Patents, they are instead used to "enhance the activity, cellular distribution or cellular uptake of the oligonucleotide." '851 Patent, 27:47-59.

100. Experiments with the PMO form of H53A(+23+47) support this. In August 2011, NS filed a patent application in which H53A(+23+47) was made as a PMO with an -OH group at the 5'-end. It was reported to induce exon 53 skipping. '217 Patent, Figure 16, Table 2. Around the same time, Sarepta scientists evaluated a modified form of H53A(+23+47) PMO, in which a cell penetrating peptide was conjugated to the 5' end. It also induced exon skipping. Sazani PCT '586, 75-76. A few years later, Sarepta scientists evaluated H53A(+23+47) PMO with a TEG tail at its 5'-end. It also induced exon 53 skipping. Bestwick PCT '240, 58-64 (TEG-modified PMO synthesis), 71 (reporting the EC_{50} value of H53A(+23+47) PMO as 9.135 μM). Collectively, these studies, obtained from different research groups, confirm that tail modifications are peripheral to the invention, and further that the inventors adequately described the claimed invention.

101. Even if, for the sake of argument, one assumes that modified bases or end modifications could unpredictably abrogate exon 53 skipping, a POSA would still have understood that the inventors possessed the claimed invention. As previously noted, I understand that the written description requirement does not demand a perfect correspondence between the members of the genus and the common structural features—it only requires a *correlation* between structure and function. Dowdy Reb. Rep. ¶106. Further, any necessary testing would have been routine. *See id.*

102. In sum, a POSA would have concluded that the specification of the Wilton Patents discloses structural features common to the members of the claimed genus such that a POSA would have been able to visualize the claimed ASOs. Dr. Hastings' contrary opinions ignore the structural features required by the claims, the disclosures of the Wilton Patents, and the general

knowledge in the art, and therefore do not change my opinion that the Wilton Patents satisfy the written description requirement.

3. The Wilton Patents Disclose a Representative Number of Species

103. As previously explained, the Wilton Patents disclose a representative species, H53A(+23+47). Dowdy Reb. Rep. ¶108. This species shares many structural features with other members of the claimed genus of the Wilton Patents. *Id*., ¶109. It is an (1) "antisense" oligonucleotide; (2) it has "20 to 31 bases"; (3) it comprises "a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA"; (4) "the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195)"; and (5) in the case of the '851 Patent, its "target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69)." *Id*. Although H53A(+23+47) was tested as a 2'OMePS ASO with uracil bases, the specification states that H53A(+23+47) can be made as a "morpholino" antisense oligonucleotide with thymine bases in place of uracil bases. *See* '851 Patent, Table 1A.

104. H53A(+23+47) is functionally representative because it "induces exon 53 skipping." Although it was tested as a 2'OMePS ASO, a POSA would have understood that the exon skipping ability exhibited by the H53A(+23+47) 2'OMePS ASO would generally translate to the corresponding H53A(+23+47) PMO. *See supra* § IV.A.2.b.iii.

105. In response, Dr. Hastings disputes both the structural and functional representativeness of H53A(+23+47). Dr. Hastings contends that H53A(+23+47) is a "pseudo-species" because it was not tested as a PMO with thymines. Hastings Supp. Rep. ¶86 (citing Wood Supp. Rep. ¶64 n.10); *see also* Hastings Supp. Rep. ¶¶¶106, 111. But the Wilton Patents expressly state that H53A(+23+47) can be made as a "morpholino" antisense oligonucleotide with thymine bases in place of uracil bases. *See* '851 Patent, Table 1A. Further, in view of the general

[redacted]

knowledge in the art, a POSA would have understood that the exon skipping activity of H53A(+23+47) 2'OMePS ASO would be maintained in its corresponding PMO format. *See supra* § IV.A.2.b.iii. Many researchers have confirmed this understanding, including, for example, [redacted], Sarepta, and NS. *See* Hastings Supp. Rep. ¶172 ([redacted]); Sazani PCT '586, 75-76 (Sarepta scientists confirming that H53A(+23+47) peptide conjugated PMO induced exon 53 skipping); '217 Patent, Figure 18 (NS scientists confirming skipping induced by H53A(+23+47) PMO, labeled "PMO No. 16").

106. Dr. Hastings also argues that H53A(+23+47) cannot be representative of the full scope of the claimed genus because it was tested without base or end modifications. Hastings Supp. Rep. ¶106. But I understand that the written description requirement does not demand examples or an actual reduction to practice (e.g., making ASOs that fall within the claimed genus). Dowdy Reb. Rep. ¶12. Further, H53A(+23+47) is structurally and functionally representative of ASOs with modified bases because both include the same core structures responsible for Watson-Crick base pairing. *See supra* § IV.A.1.b.ii. It is also representative of ASOs with different end modifications, as end modifications are not core structural features of the claimed ASOs and do not participate in Watson-Crick base pairing (and are not even recited in the claims). *See supra* § IV.A.1.b.iii.

107. Dr. Hastings also contends that the reported skipping activity of H53A(+23+47) ("very faint skipping to 50 nM") does not meet the definition of "efficient antisense molecule" provided in the Wilton Patents. Hastings Supp. Rep. ¶86; *see also id.*, ¶111. But the claims of the Wilton Patents simply recite that the claimed ASOs "induce[] exon 53 skipping." Moreover, a POSA reading the Wilton Patents would have understood that any exon skipping was a meaningful

[redacted]

not available in June 2005, and thus could not reflect the understanding of a POSA as of that time. Wilton PCT '350, item (22). Notably, Dr. Hastings has been ***unable to identify or even deliberately design*** any ASO meeting the structural characteristics of the claims that does not induce skipping of exon 53. *See generally* Hastings Supp. Rep.

120. *Third*, numerous studies from multiple independent research groups repeatedly confirmed Dr. Wilton's exon 53 hot spot. *See* Dowdy Reb. Rep. § V.A.2.c. For example, regardless of whether or not [redacted], it indisputably induces exon 53 skipping. *See supra* § IV.A.3.

121. In sum, Dr. Hastings' attack against Dr. Wilton's ***exon 53*** hot spot based on ***exon 3*** or ***exon 43*** targeting ASOs is a red herring.

b. Dr. Hastings' Reinterpretation of [redacted]

122. Dr. Hastings again relies on [redacted]. Hastings Supp. Rep. ¶157. In my Rebuttal Report, I addressed each study and explained that [redacted] supports my opinion that the Wilton Patents satisfy the written description requirement. Dowdy Reb. Rep. ¶¶188-220. Specifically, I explained that these studies demonstrate [redacted]. *Id.*, ¶211.

123. The Court's clarified claim construction further strengthens my opinion, in that [redacted]. *See supra* § III.B. As shown below, [redacted]:

[redacted]

Tested Oligonucleotide	Length	Design Rationale	Skipping	In Claim Scope
[redacted]				

Table 3. Summary of the [redacted]
(adapted from Hastings Supp. Rep. ¶172; * = in scope of the '590 and '827 Patent claims)

[redacted]

Tested Oligonucleotide	Length	Design Rationale	Skipping	In Claim Scope
[redacted]				

Table 4. Summary of [redacted]
(adapted from Hastings Supp. Rep. ¶177)

124. In her Supplemental Report, Dr. Hastings attempts to reinterpret the [redacted] data and contends that "these data supports [sic] my opinions above in several ways." Hastings Supp. Rep. ¶¶174, 179, 180. They do not.

125. For instance, Dr. Hastings contends that [redacted] they generally confirm the unpredictability of achieving exon skipping in exon 53 and that having 12 consecutive bases will not reliably induce exon skipping." Hastings Supp. Rep. ¶¶174, 179.

126. But Dr. Hastings wrongly conflates [redacted]

[redacted]

127. In her "reexamination," Dr. Hastings again fails to interpret the data in the context of the claimed inventions of the Wilton Patents. In asserting that [redacted] (Hastings Suppl. Rpt. ¶ 174), Dr. Hastings was referring to [redacted] they do not undermine the correlation between the ***claimed*** structural features and the ***claimed*** function of exon 53 skipping. *See* Dowdy Reb. Rep. ¶11 (the written description requirement is satisfied when the specification discloses "structural features common to the members of the genus such that a POSA can visualize or recognize the members of the genus"). Indeed, contrary to Dr. Hastings' reexamination, the [redacted] data provides a powerful confirmation of the importance of the claimed invention and the strong structure/function correlation.

[redacted]					
Tested Oligonucleotide	**Length**	**Design Rationale**	**12 Bases**	**ASO 100% Complementary**	**Skipping**
[redacted]					

Table 5. Summary of the [redacted]
(adapted from Hastings Supp. Rep. ¶172)

128. Focusing on the '851 Patent specifically, Dr. Hastings also contends that [redacted]

[redacted]

[redacted] Hastings Supp. Rep. ¶¶174, 179-180. But Dr. Hastings commits the same error of drawing conclusions based on [redacted]

[redacted]

Tested Oligonucleotide	Length	Design Rationale	+36+42	ASO 100% Complementary	Skipping
[redacted]					

Table 6. Summary of the [redacted]
(adapted from Hastings Supp. Rep. ¶172)

129. Dr. Hastings also contends that [redacted]

Hastings Supp. Rep. ¶180. As construed by the Court, the claims of the Wilton Patents "requires 100% complementarity to consecutive bases of a target region of exon 53 throughout the entire length of the antisense oligonucleotide." *See supra* § III.B. As Dr. Hastings acknowledges (*see* Hastings Supp. Rep. ¶180), [redacted] As such, it is irrelevant [redacted]

130. In sum, the [redacted] data confirms the structure/function correlation disclosed and claimed in the Wilton Patents. Dr. Hastings' reinterpretation of that data focuses on

[redacted], and is therefore irrelevant.

B. The Wilton Patents Satisfy the Enablement Requirement

131. In my Rebuttal Report, I opined that the Wilton Patents satisfy the enablement requirement. *See* Dowdy Reb. Rep. § V.B. Primarily relying on Dr. Wood, Dr. Hastings raises several new arguments in her Supplemental Report, most of which ignore the Court's revised construction of the term "base sequence." *See supra* § III.B. Regardless, as discussed below, these new arguments do not change my opinion that the Wilton Patents are enabled because Dr. Hastings fails to consider the state of the art as a whole and wrongly equates "unpredictability" with "experimental variability." If anything, her new arguments reinforce my opinion that the amount of experimentation needed to make and use the claimed inventions of the Wilton Patents would have been reasonable and not undue.

1. The Breadth of the Claims of the Wilton Patents and the Nature of the Invention

132. The scope of the claims of the Wilton Patents is narrow. *See supra* § IV.A.1.a. The claims are directed to a limited group of structurally defined ASOs corresponding to a discrete set of target regions within exon 53. *Id*. In the case of the '851 Patent, the claims encompass 168 distinct target regions, all of which fall squarely within the exon 53 hot spot. *Id*. In the case of the '590 and 827 Patents, the claims encompass 330 distinct target regions, all of which fall within or significantly overlap with the exon 53 hot spot. *Id.* Consequently, the number of ASOs that a POSA would need to make and test is limited. *Id.*

133. In her Supplemental Report, Dr. Hastings contends that the claims of the Wilton Patents are "structurally . . . broad" because the claims encompass "no fewer than tens of thousands of antisense oligonucleotides, and likely at least millions." Hastings Supp. Rep. ¶184. I disagree.

[redacted]

The claimed ASOs of the Wilton Patents are structurally uniform because they are defined by multiple structural features—length (20 to 31 bases), complementarity (100%), backbone chemistry (morpholino), type of bases (thymines in place of uracils), and target region (exon 53 hot spot). The features focused on by Dr. Hastings are either outside the scope of the claims (intersubunit linkages) or peripheral to exon skipping functionality (end modifications). *See supra* § IV.A.1.b. Moreover, even if a POSA used ASOs with non-natural bases, only a limited number of non-natural bases were available, each of which must maintain the structural features (e.g., core pyrimidine structure) necessary for Watson-Crick base-pairing. *See id*.

134. Dr. Hastings also contends that the claims of the Wilton Patents are "functionally broad" because they encompass ASOs that exhibit "very faint skipping" to "a therapeutic effect." Hastings Supp. Rep. ¶184. I again disagree. The claims of the Wilton Patents require a specific function—"induc[ing] exon 53 skipping." To confirm whether a candidate ASO induces exon 53 skipping, a POSA would use routine assays disclosed in the specification and known in the art. That the claims of the Wilton Patents may encompass ASOs with varying abilities to induce exon 53 skipping does not change the scope of experimentation required.

135. Relying on Dr. Wood, Dr. Hastings contends that "a POSA would need to screen each antisense oligonucleotide in order to determine if it induces exon 53 skipping as required by the [Wilton] Patent claims" and thus, "the number of potential antisense oligonucleotides that one would need to screen . . . is vast." Hastings Supp. Rep. ¶185; *see id*., ¶194 ("each potential morpholino antisense oligonucleotide would need to be tested to determine if it induces exon 53 skipping"). I again disagree. As an initial matter, Dr. Hastings incorrectly assumes that some experimentation would be needed to make and use the claimed inventions of the Wilton Patents. But as discussed above, a POSA would have understood that most, if not all, candidate ASOs

[redacted]

would induce exon 53 skipping because they are directed to the exon 53 hot spot disclosed in the Wilton Patents. This structure-function relationship eliminates, or at least significantly reduces, the amount of experimentation required. Consistent with this, despite having prepared 5 expert reports in this case, Dr. Hastings has not offered any real-world evidence of ASOs meeting the structural requirements of the claims that do not induce exon 53 skipping. *See generally* Hastings Supp. Rep.

136. That said, even if some confirmatory experimentation would be needed, a POSA would not need to test every possible candidate ASO. Rather, a POSA would have prioritized candidate ASOs and then rationally focused on groups of ASOs. For example, a POSA could first test groups of 20-mers, 25-mers, and 31-mers for exon skipping, which would inform a POSA about the exon skipping of PMOs of intervening lengths. *See supra* § IV.A.1.c. Even if a POSA were to comprehensively screen, the limited number of target regions (e.g., 168 for claim 1 of the '851 Patent) means this would be routine. If desired, a POSA could derivatize tested PMOs with one or more modified bases or end modifications to improve cellular uptake and binding affinity, as taught by the Wilton Patents. This process would have been straightforward, as it used only routine methods of making and testing PMOs and standard laboratory equipment. *See* Dowdy Reb. Rep. ¶¶272-288. Contrary to Dr. Hastings' assertion, "the number of potential antisense oligonucleotides that one would need to screen" would ***not*** have been "vast." *See* Hastings Supp. Rep. ¶185.

2. The Relative Skill of Those in the Art

137. In my Rebuttal Report, I explained that the relative skill of those in the art was high. Dowdy Reb. Rep. ¶232.

138. Dr. Hastings' definition of a POSA, which I understand the parties have adopted, reinforces my opinion. *See supra* § III.A. Here, the POSA possesses "expertise in molecular

[redacted]

DATE: August 14, 2024

By: _____
Steven F. Dowdy, Ph.D.